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Cell Renewal in Noncornified and Cornified Buccal Epithelium in the Rabbit

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This study was undertaken to compare some aspects of cell renewal in the noncornified and cornified epithelia that are juxtaposed in the buccal mucosa of the rabbit. Specimens were analyzed by autoradiography and scintillation counting at various times after the injection of tritiated thymidine or tritiated proline. In the noncornified epithelium, the labeling index in the proliferative compartment at 1 hr was 15.5%; in the entire cell population, it was 5.8% at 1 hr, 10.4% at 24 hr, and 20.2% at 72 hr. The leading edge of labeled cells reached the surface by 96 hr. In the cornified epithelium, the labeling index in the proliferative compartment was 8.7% at 1 hr; in the entire nucleated cell population, it was 4.2% at 1 hr, 9.2% at 24 hr, and 12.1% at 96 hr. The leading edge of labeled cells reached the stratum corneum by 96 hr and the surface by 144 hr. It was concluded that renewal occurs at a more rapid rate in the noncornified than in the cornified epithelium under study.

In humans and other species, the oral mucosa is covered by a noncornified stratified squamous epithelium in some regions and by a cornified one in others. Many morphologic, histochemical, and biochemical differences between the 2 types of oral epithelium have been described [1–3], but direct comparisons of cell renewal have been scanty. Information about cell renewal in these 2 epithelia should be helpful in the understanding of the process of cornification and the development and healing of some lesions of the oral mucosa.

The rabbit is one of the species with both types of oral epithelium, and it is the only commonly used laboratory nonprimate suitable for comparative studies since all of the oral epithelium of rodents is cornified. However, the large size of the rabbit makes any experiment with labeled thymidine expensive, and therefore the number of animals and the scope of the study were restricted.

Our findings indicate that, in the buccal mucosa of the rabbit, renewal takes place at a considerably more rapid rate in the noncornified than in the cornified epithelium.

MATERIALS AND METHODS

Male Dutch rabbits, weighing 625 to 1,180 gm, were used in this experiment. In each of one group of rabbits, tritiated thymidine (^{3}H-TdR; Schwarz/Mann, methyl labeled, specific activity of 0.36 Ci/mmole, concentration of 1 mCi/ml) in sterile aqueous solution was injected into an ear vein at a dose of 1 mCi/kg. Tritiated L-proline (Schwarz/Mann, specific activity of 3 Ci/mmole, concentration of 1 mCi/ml) was injected into a second group of animals (1 mCi/kg body weight) to determine the transit time of cells through the stratum corneum [4,5].

All injections were made between 8:45–9:30 AM to avoid the effects of diurnal variation on cell renewal. Animals that had been injected with ^{3}H-TdR were killed by decapitation at the following time periods after injection: 4 at 1 hr, 2 at 1 day, 3 at 2 days, 2 at 3 days, and 3 at 4 days. Those injected with ^{3}H-proline were killed as follows: 1 at 1 hr, 2 at 2 days, and 2 at 5 days. After an animal was killed, the buccal mucosa from both sides was quickly dissected out. The specimens extended from just anterior to the ramus of the mandible to the area of the commissure of the lips and from the upper to the lower buccal sulcus. The specimen for autoradiographic study was taken from one side. Since rabbit buccal epithelium is noncornified in the region of the molar teeth and cornified just anterior to this region, it contained both types of epithelium separated by a narrow transitional zone. The specimen from the other side was used for quantitation of thymidine uptake. It was freed of muscle as close as gross inspection permitted. The cornified and noncornified mucosa were isolated from the transitional zone, and then frozen in liquid nitrogen for subsequent assay.

Autoradiography

For autoradiography, 4 μm-thick sections were prepared from paraffin-embedded specimens. Care was taken to section the specimens perpendicular to the epithelial surface. After deparaffinization, the mounted sections were dipped in Kodak NTB-3 emulsion, diluted 1:1, and placed in light-tight black plastic boxes which contained silica gel. They were exposed for 14 days at 4°C, then developed (Kodak D-19), fixed, and stained with hematoxylin and eosin. Counts and measurements were performed on sections that were 200 μm apart. Only broad epithelial ridges were examined in order to reduce the possibility of sampling tangentially cut portions of epithelium.

Labeling Indices (LI)

Labeled and unlabeled nuclei were counted on sections magnified 1000× using an oil immersion objective and an ocular grid. A nucleus was considered labeled if it had at least 3 grains above it. Background labeling was low enough that this number seemed to ensure the exclusion of false positives. This count was considered sufficiently low that the minimum of 3 grains as the criterion of labeling would not result in an unacceptably high number of false negatives. Two LI's were obtained for each region. One was the percentage of labeled nuclei in the proliferative compartment at 1 hr postinjection. In both epithelia, the deepest 1-2 rows of spinous cells as well as the basal cells, but no others, contained labeled nuclei 1 hr after the injection of ^{3}H-TdR; these rows were considered the proliferative compartment.

LI's were based on counts of from 575 to 6,450 total nuclei (mean, 1,850), of which 75-610 were labeled (mean, 192), per region in each animal. Means were compared by Student's *t*-test [6], and differences were considered significant if they were at the 5% level or less.

The distribution of labeled nuclei as a function of position along the length of the basement membrane was compared to the distribution predicted by Poisson statistics, and the distribution between basal and lower spinous cells was noted.

Transit Times

Minimal transit times were expressed as the number of cell rows traversed or as the distance traveled by the leading edge of labeled cells. The number of rows traversed and the total number of rows of

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Abbreviations:
^{3}H-TdR: tritiated thymidine
LI: Labeling indices

nucleated cells were counted directly at 400×. The distance traveled and the thickness of the epithelium were measured by using a calibrated ocular insert. A total of 10–15 counts and measurements were made in 3–4 sections of each region.

Comparisons on the basis of rows traversed are not affected by the different vertical dimensions of cells in cornified and noncornified regions. They can, however, not be made for the stratum corneum, even if a cytoplasmic label were used, since the rows of residues cannot be discerned in sections stained with hematoxylin and eosin. For this reason, minimal transit times were also determined on the basis of distance traveled. ^{3}H-TdR could not be used to measure passage through the stratum corneum, since nuclei are no longer present. ^{3}H-proline was used instead. It is present in the cytoplasm of all nucleated cells 1 hr after injection [4] and was retained as cell residues passed through the stratum corneum. Thus, in noncornified and cornified epithelium, transit time based on distance traveled through the nucleated part of the epithelium was determined on ^{3}HTdR-labeled sections, and through the stratum corneum of cornified epithelium it was determined on ^{3}H-proline-labeled sections.

Assay of ^{3}H-TdR Uptake

Mucosal samples were placed on Whatman No. 1 ashless filter paper, dried, weighed and combusted in an automatic oxidizer.* The tritiated water from each sample was collected in a scintillation vial to which was added 15 ml of scintillation fluor [5 gm PPO (2,5-diphenyloxazole), 0.3 gm POPOP (1,4-bis-2 [5-phenyloxazolyl-2]-bezene), 135 ml toluene, 720 ml dioxane, and 15 ml absolute methanol]. The samples were counted in an ambient temperature liquid scintillation spectrometer.† Recovery of tritium as water was consistently reproducible and generally greater than 95%. Tritiated toluene was used as a reference standard and the counting efficiency for tritium was approximately 40%, with a background of 20–25 counts per minute. This efficiency factor was used to convert our collected data from counts per minute to disintegrations per minute or microcuries per unit weight of tissue.

The concentrations at 1 hr will not be given because of the strong possibility that unincorporated ^{3}H-TdR was still present. By 24 hr, unincorporated ^{3}H-TdR would have fallen to an insignificant level [7].

RESULTS

Labeling Index

In the proliferative compartment, the LI at 1 hr postinjection was higher in the noncornified than in the cornified region in all 4 pairs of epithelia (Table I). The mean in the noncornified epithelium (15.5%) was almost twice that in the cornified (8.7%).

In the entire nucleated cell population, the noncornified LI was higher than the cornified one in 13 of 14 pairs of regions, and the mean at each time interval was greater (Table II). The difference increased with time because the rate of increase in LI was far greater in the noncornified epithelium. There the LI had increased from 5.8% at 1 hr to 20.2% by 72 hr, whereas in the cornified it had increased from 4.2 to 10.8% in the same time interval. At 96 hr, the LI had already decreased in the noncornified epithelium, but in the cornified it continued its slow increase.

Distribution of Labeled Cells

The care taken to ensure sectioning perpendicular to the surface and the restricting of counts and measurements to broad epithelial ridges minimized the possibility of artifacts due to tangential sectioning. As mentioned, labeled cells were found in the basal and first and second rows of spinous cells (Figure). In the noncornified epithelium approximately 45% were in the basal row, whereas in the cornified 49% were located there. When the distribution of labeled cells along the basement membrane was compared with that predicted by Poisson statistics, there was suggestive, but statistically insufficient evidence to establish clustering. We have assumed a random distribution.

TABLE I. *Labeling indices in proliferative compartments of buccal epithelium in 4 rabbits 1 hr after injection of ^{3}H-TdR*

	Noncornified	Cornified
	13.3%	10.4%
	20.2%	8.2%
	15.5%	8.6%
	12.8%	7.7%
Mean	15.5%	8.7%
SEM	1.68	0.58

TABLE II. *Labeling indices (%) in entire nucleated cell populations in rabbit buccal epithelium*[a]

Hours after ^{3}H-TdR injection	Rabbit No.	Noncornified		Cornified	
		LI	Mean ± SEM	LI	Mean ± SEM
1	1	5.2		4.7	
	2	6.1		4.0	
	3	6.3		4.1	
	4	5.7		4.0	
			5.8 ± 0.22		4.2 ± 0.14
24	5	8.9		9.7	
	6	11.8		8.6	
			10.4 ± 1.44		9.2 ± 0.54
48	7	13.9		11.9	
	8	18.6		8.5	
	9	17.5		9.5	
			16.7 ± 1.41		10.0 ± 1.00
72	10	22.5		12.1	
	11	17.9		9.4	
			20.2 ± 2.30		10.8 ± 1.34
96	12	14.9		11.6	
	13	18.4		11.4	
	14	18.0		13.4	
			17.1 ± 1.10		12.1 ± 0.63

[a] The difference between mean LI's at 1 hr is significant. In noncornified, differences between LI's at 1 and 24 hr and between LI's at 24 and 72 hr are significant. In cornified, differences between LI's at 1 and 24 hr and between LI's at 24 and 96 hr are significant.

Minimum Transit Times

In the noncornified epithelium the patterns of progress of the leading cells were strikingly similar whether based on cell rows traversed or distance traveled (Table III). Passage through the epithelium was comparatively slow during the first 48 hr, approximately 25% (9 of 38 rows, 83 of 347 μm) having been traversed. During the 48 hr–72 hr interval, the rate of advance increased dramatically. The leading cells had passed through approximately 70% more of the epithelium and were one row from the surface. Labeled nuclei were at the surface at 96 hr in 2 of 3 rabbits, and one row away in the third.

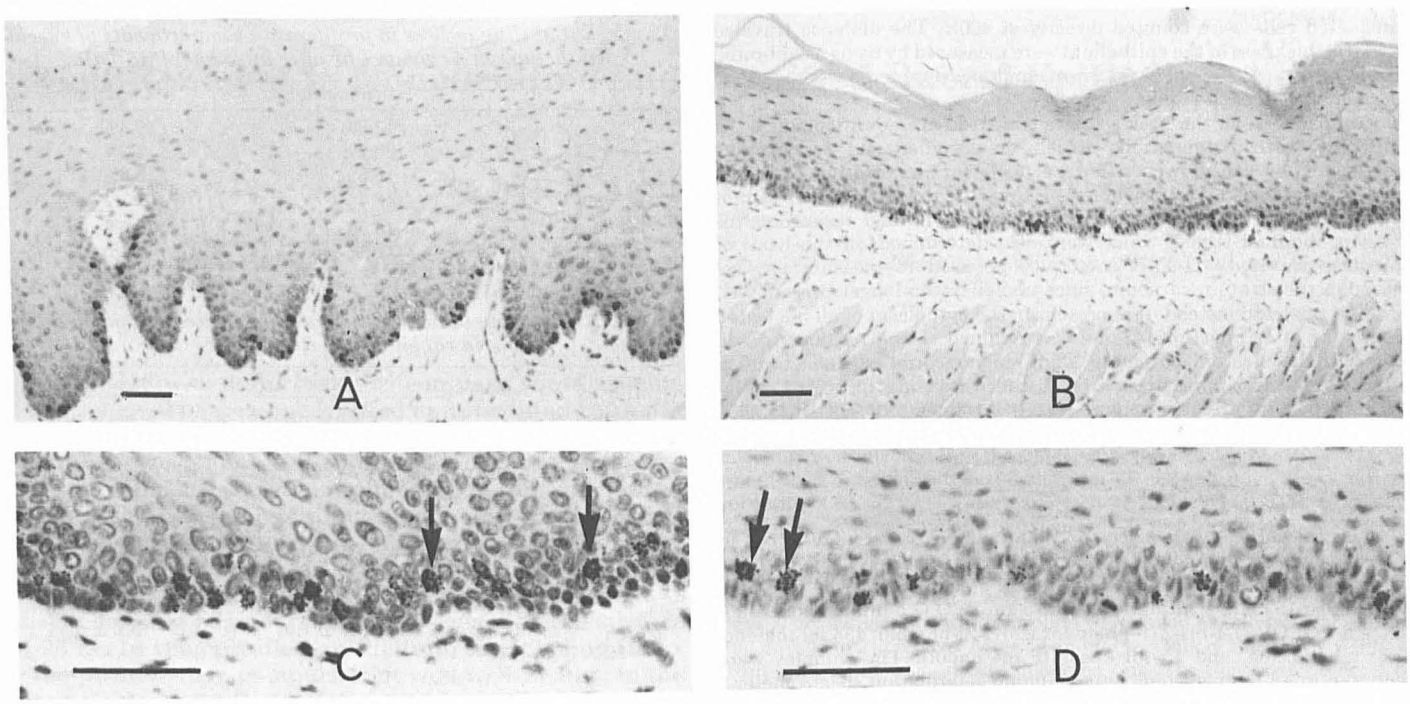
In the cornified epithelium, the rate of advance during the first 24 hr was similar to that in the noncornified. However, in contrast to the noncornified epithelium, the rate thereafter increased only slowly and did not change markedly. The rate in cornified epithelium on the basis of rows traversed seemed to increase after 48 hr, but far less so than in noncornified epithelium. The leading cells had traversed the nucleated cell part of the epithelium by the end of 96 hr.

Passage of cell residues through the stratum corneum was studied in sections from animals that had been injected with ^{3}H-proline. At 1 hr, there was label in the cytoplasm of all nucleated cells, but none in the stratum corneum. The next sections available for examination were from rabbits killed at 48 hr postinjection. Label was present throughout the stratum corneum. Hence, passage of the fastest moving residues through it had occurred within that time period, and passage through the entire cornified epithelium took approximately 144 hr.

The differences in minimal transit times that were noted between the 2 types of epithelium were consistent in all of the animals studied.

* Packard Tritium Oxidizer, Model 305, Packard Instruments Co., Downers Grove, Illinois.

† Beckman DPM 100, Beckman Instruments, Inc., Fullerton, Ca.



Rabbit buccal mucosa 1 hr after injection of ^{3}H-TdR. Hematoxylin and eosin. *A* and *C* are noncornified, *B* and *D* are cornified. Marker = 20 μm. Labeled cells are more concentrated in noncornified epithelium. Labeled cells (*arrows*) are present in deepest spinous cells in both types of epithelium.

TABLE III. *Advance of leading edge of cells labeled with ^{3}H-TdR through rabbit buccal epithelium (means from indicated number of animals ± 1 SEM)*

Hours after ^{3}H-TdR injection	Noncornified						Cornified					
	Rows			Thickness (μm)			Rows			Thickness (μm)		
	Edge	Entire epith.	%	Edge	Entire epith.	%	Edge	Entire epith.[a]	%	Edge	Entire epith.[b]	%
1 (n = 4)	2.7 ±0.15	39.4 ±1.67	6.9 ±0.56	21.5 ±1.37	509.6 ±25.82	4.3 ±0.38	2.2 ±0.17	13.8 ±1.17	16.3 ±0.89	18.9 ±1.56	146.1 ±13.59	12.9 ±0.25
24 (n = 2)	4.2 ±0.65	35.8 ±1.15	11.7 ±2.20	35.6 ±5.45	416.2 ±22.90	8.7 ±1.75	3.0 ±0.05	12.4 ±0.20	23.8 ±0.80	28.3 ±1.60	144.1 ±12.70	19.7 ±0.60
48 (n = 3)	9.2 ±1.97	37.6 ±1.75	24.2 ±4.26	83.1 ±22.51	346.9 ±27.04	23.3 ±4.87	5.1 ±0.20	13.8 ±0.61	37.0 ±0.72	32.1 ±3.09	99.9 ±5.23	32.0 ±1.37
72 (n = 2)	35.0 ±1.70	36.3 ±0.45	96.5 ±3.5	401.7 ±42.6	426.4 ±26.95	96.1 ±3.90	9.2 ±1.65	12.9 ±1.35	70.7 ±5.45	59.8 ±15.30	106.2 ±18.80	55.5 ±4.60
96 (n = 3)	36.2[c]	37.8[c]	98.6[c] ±1.43	503.2[c]	524.7[c]	98.6[c] ±1.37	13.0 ±0.94	13.4 ±1.03	97.0 ±1.11	90.8[d] ±6.62	127.7 ±10.02	71.2 ±1.05

[a] Nucleated cell population only; does not include stratum corneum.
[b] Entire thickness, including stratum corneum.
[c] Data obtained for 1 rabbit only. In the other 2, labeled cells were at surface at 96 hr and measurements were not made. Percentages derived from 2 animals @ 100% and 1 @ 96%.
[d] Junction of nucleated part of epithelium and stratum corneum. ^{3}H-proline-labeled cell residues were at surface at 48 hr after proline injection.

^{3}H-TdR Assays

The concentration of ^{3}H-TdR was greater in the noncornified mucosa than in the cornified at all time intervals and in all rabbits (Table IV). In the noncornified, it remained constant from 24 hr through 72 hr, and was more than twice as high as in the cornified. At 96 hr it had decreased significantly. In the cornified, the concentration remained constant in the 24–96 hr interval.

TABLE IV. *Mean concentration of ^{3}H-TdR (μCi × 10^{-3}/mg dry weight ± 1 SEM) in rabbit buccal mucosa*

Hours after ^{3}H-TdR injection	n	Noncornified	Cornified
24	2	2.09 ± 0.05	0.93 ± 0.11
48	3	2.15 ± 0.18	0.91 ± 0.06
72	2	2.03 ± 0.16	0.81 ± 0.02
96	3	1.47 ± 0.07	0.97 ± 0.18

DISCUSSION

Stratified squamous epithelium is an example of a constantly renewing cell system. Cells are produced in the proliferative compartment, move out into the functional compartment, and then to the surface, where they are shed. Since the rate of cell loss at the surface is balanced by the rate of cell production, on the average one of the daughter cells remains in the proliferative compartment and the other moves into the functional compartment.

Most of the studies of the kinetics of cell renewal in oral epithelium have been in rodents [8–13]. Since all rodent oral epithelium is cornified, the extrapolation of findings in rodents to humans is not well founded. The 2 previous studies on cell renewal kinetics in the oral epithelium of rabbits do not permit direct comparisons with the present results. Henry and his coworkers [14] reported a mean mitotic index of 5.1% in noncornified buccal epithelium. They did not study cornified epithelium. From Gigoux's data [15], it is possible to compare a noncornified region with a fully cornified one in only one rabbit. The mitotic index in the noncornified buccal epithelium was 7.45/mm surface length, and in the cornified epithelium of the hard palate it was 1.12.

More recently, reports have been published dealing with cell renewal in human (noncornified) buccal epithelium. Kaidbey and Kurban [16] and Alvares et al [17] incubated mucosal

samples with ^{3}H-TdR and obtained LI's of 7.5% and 7.6%, respectively, in the proliferative compartment. Gillespie [18] studied the LI *in vivo* in 5 terminally ill humans and observed an LI of 12.6% in the basal cells only. The study of Demetriou and Ramfjord [19] most closely approximates ours, although their observations were limited to labeled nuclei in the basal layer only. In Rhesus monkeys, 1 hr after injection, they observed LI's of 14.7% in the noncornified epithelium of the alveolar mucosa and 7.9% in the adjacent cornified epithelium of the attached gingiva. The magnitude and ratio of these values agrees well with that of our indices of 15.5% and 8.7% respectively, although ours are based on the entire proliferative compartment (Table I).

Assuming for the sake of an estimate that DNA synthesis times are equal, the turnover times in the 2 proliferative compartments are inversely related to the labeling indices, or only half as long (8.7%/15.5%) in the noncornified as in the cornified epithelium. From our data it cannot be decided whether the higher labeling index is due to a larger progenitor compartment, to a larger growth fraction, or to a shorter time interval between the divisions of the participating cells. Reports indicate a growth fraction of unity in epidermis [20,21]. However this may be, the greater labeling index in the noncornified than in the cornified epithelium means that more cells are being produced in the former, unless it can be shown that noncornified DNA synthesis time is proprotionately longer. DNA synthesis times were not determined in this study, but no data presented in the literature suggest that it is longer in a noncornified epithelium [22].

On the same assumption of equal DNA synthesis times, it is also possible to estimate the relative turnover times in the 2 epithelia from the LI's in the proliferative compartments and the LI's in the entire populations of nucleated cells. The LI in a given proliferative compartment (P) and the LI in the associated entire population (i.e., proliferating plus differentiating compartments; P + D) are calculated from the same labeled nuclei. Thus, the relative sizes of the total populations containing these labeled nuclei can be determined from the relation

$$(LI_P) \times (P) = (LI_{P+D}) \times (P + D).$$

For noncornified epithelium,

$$0.155\ P = 0.058\ (P + D),$$

$$\frac{P}{P + D} = \frac{1}{2.7}, \text{ and}$$

$$\frac{P}{D} = \frac{1}{1.7}.$$

Similarly, for cornified epithelium,

$$0.087\ P = 0.042\ (P + D),$$

$$\frac{P}{P + D} = \frac{1}{2.1}, \text{ and}$$

$$\frac{P}{D} = \frac{1}{1.1}.$$

Since proliferative compartment turnover times are inversely related to their LI's, the ratio of proliferative compartment turnover times in noncornified to cornified epithelium is 8.7 to 15.5. The ratio of turnover time in the differentiating compartment to that in the proliferative compartment is related to the populations in the 2 compartments. Computations on this basis show that the turnover time in the noncornified epithelium is less than that in the nucleated part of the cornified epithelium:

$$\frac{\text{Noncornified}}{\text{Cornified}} = \frac{8.7 \times \frac{1.7}{1}}{15.5 \times \frac{1.1}{1}} = \frac{14.8}{17.1}$$

It must be remembered, however, that the stratum corneum is not included in this estimate. The turnover time in the cornified epithelium, thus, is even longer than in the noncornified, by that (unknown) amount. This is reflected in the slower rate of advance of labeled cells in cornified epithelium.

At each time interval, the LI in the entire population of noncornified epithelium was greater than that in the nucleated part of the cornified one. If the cell residues in the stratum corneum could have been counted, the cornified LI's would have been smaller and the differences at each interval probably would have been statistically significant.

In both types of epithelium, the LI in the entire population of cells had approximately doubled in the 1 hr–24 hr interval. This doubling represents the passage of the initially labeled cells through the remaining portion of S and through G_2 and M, and probably was completed no later than 12–14 hr after injection. In the noncornified epithelium, the LI had increased from 5.8% at 1 hr to 20.2% at 72 hr, a 3.5-fold increase. In the cornified epithelium the increase in the same time span was from 4.2% to 10.8%, a 2.6-fold increase; at 96 hr it was to 12.1%, a 2.9-fold increase. The increases beyond the first doubling are most probably due to further passage through the cell cycle of initially labeled cells, since assays showed no increase in ^{3}H concentration during the course of the study and re-utilization of DNA would account for only a small part of the increase. These further passages through the cell cycle proceeded more rapidly in the noncornified epithelium. Their occurrence could have been confirmed by grain counts over the labeled nuclei, but our experimental design did not provide for grain counts to be done. The slower rate of advance towards the surface by the leading edge of labeled cells during the first 48 hr than during the subsequent 24 hr is compatible with further divisions of the labeled cells. Iverson, Bjerknes, and Devik [23] describe a residence time of about 60 hr in the basal layer for newly differentiated cells of mouse epidermis. In oral epithelium, there appears to be movement of some initially labeled cells within 24 hr.

The consistently higher tritium concentration in noncornified mucosa corresponds with the consistently higher LI's in that region. In the noncornified mucosa, the concentration had decreased between 72 and 96 hr, corresponding to the period in which autoradiographs indicated that labeled cells had reached the surface and were shed. In the cornified mucosa, the tritium concentration remained constant during the 96 hr period, which is consistent with labeled cells having just reached the stratum corneum during that time. It can be argued that the data for tritium do not represent the actual situation in the 2 epithelia, since the relative contributions of epithelium and supporting tissue are unknown. However, this is equally true for both types of mucosa, and thus the data do yield a close approximation to the actual ratios of epithelial tritium levels.

The relative rates of advance of the fastest moving cells in cornified and noncornified oral epithelium have not been described previously. The tremendous increase in rate in the noncornified epithelium in the 48 hr–72 hr interval set it clearly apart from the cornified region. These differences may reflect differences in desmosomal attachments. Chen [24] found that, in the rabbit, the proportion of adjoining cell membranes occupied by desmosomes is 40–60% smaller in noncornified oral epithelium than in cornified, and the difference is most pronounced in the outer half of the epithelia. The looser attachment of the noncornified cells would permit their more rapid migration.

The care that was taken in orienting the specimens and in avoiding the examining of tangentially cut areas left no doubt that labeled nuclei and hence DNA synthesis occurred in the deeper spinous cells as well as in basal cells. The proliferative compartment in both regions comprised the deepest 2–3 rows of cells. Kaidbey and Kurban [16] and Alvares et al [17] observed proliferative compartments made up of the 3 deepest rows. The mean number of rows in our material was 2.7 in noncornified and 2.2 in cornified epithelium (Table III), possibly

reflecting the differences in total numbers of cell rows in the 2 epithelia. The observation that proliferating oral epithelial cells are not confined to the basal layer coincides with the observations on many species in most recent investigations [2].

In summary, the data presented here indicate that cell renewal occurs at a more rapid rate in the noncornified epithelium than in cornified. In the noncornified epithelium, we observed a higher LI, a higher uptake of ^{3}H-TdR, and the passage of the fastest moving cells through it in 2/3 the time required to move through the cornified epithelium. The proximity of these 2 epithelia eliminates the possibility of the differences being due to individual variation or differences in location, and supports the contention that the differences are related to cornification.

The primary function of oral epithelium is protection of the underlying tissues, and this depends on the integrity of the epithelium. The greatest threat to its integrity is mechanical trauma from food and, in some regions, from the teeth. Cornified epithelium has many structural features, including the resistant stratum corneum, that provide it with inherent toughness and enable it to withstand these potentially damaging forces [3]. Noncornified epithelium does not have a resistant stratum corneum. Its surface cells are more susceptible to damage and loss, and one of the ways by which it may maintain its integrity is by a greater rate of cell turnover.

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